Response Under 37 C.F.R. §1.192
Appellant's Brief

Application No. 10/057,629
Paper dated: June 6, 2005
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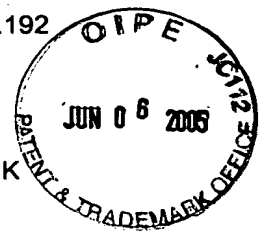

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re:	Patent Application of Harry R. Davis	: PATENT APPLICATION
Serial No.:	10/057,629	: Group Art Unit: 1617
Filed:	January 25, 2002	: Examiner: San Ming R. Hui
For:	Use of Substituted Azetidinone Compounds for the Treatment of Sitosterolemia	: :Atty. Docket No.: CV01382K

MAIL STOP APPEAL BRIEF – PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ON APPEAL FROM THE PRIMARY EXAMINER TO THE
BOARD OF PATENT APPEALS AND INTERFERENCES

APPELLANT'S BRIEF UNDER 37 C.F.R. § 1.192

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I

REAL PARTY IN INTEREST

The real party in interest in this Appeal is assignee Schering Corporation, having a principal place of business 2000 Galloping Hill Road, Kenilworth, NJ 07033.

II

RELATED APPEALS AND INTERFERENCES

As the legal representative of Appellant, the undersigned attorney has no knowledge of any appeals or interferences directly related to this Appeal.

III

STATUS OF CLAIMS

This is an original patent application in which claims 1-47 and 53-58 are pending in this application. Claims 2-7, 12, 25-31, 46, 57 and 58 have been withdrawn from consideration by the Examiner as being non-elected.

Claims 1, 8-11, 13-24, 32-45 and 53-56 (pending) were finally rejected rejected under 35 U.S.C. §103(a) as obvious over US 5,846,966 ("Rosenblum et al.") in view of Belamarich et al. (Pediatrics, 1990; 86(6):977-81 in an Office Action mailed February 8, 2005 ("Final Office Action") and Advisory Action mailed May 20, 2005 ("Advisory Action").

Thiry-five (35) pending claims (1, 8-11, 13-24, 32-45 and 53-56) are at issue in this Appeal.

IV

STATUS OF AMENDMENTS

No claims were amended after final rejection. A copy of the claims involved in this Appeal is contained in the Appendix attached hereto.

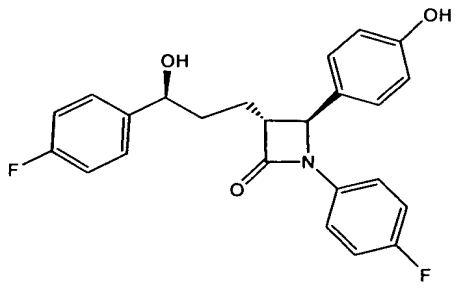
V

SUMMARY OF CLAIMED SUBJECT MATTER

In one embodiment set forth in claim 1, Applicants have discovered a method of treating sitosterolemia, comprising administering to a mammal in need of such treatment an effective amount of at least one sterol absorption inhibitor, or pharmaceutically acceptable salt or solvate of the least one sterol absorption inhibitor, or prodrug of the at least one sterol absorption inhibitor or pharmaceutically acceptable salt or solvate of the least one sterol absorption inhibitor, or mixture thereof. See original claim 1, and page 2, lines 11-16 of the specification.

In another embodiment set forth in Claim 24, Applicants have discovered a method of treating sitosterolemia comprising administering to a mammal in need of such treatment:

(a) an effective amount of a sterol absorption inhibitor represented by Formula (VIII) (ezetimibe):



(VIII)

and

b) an effective amount of atorvastatin and/or simvastatin.

In another embodiment set forth in Claim 32, Applicants have discovered a method of treating sitosterolemia, comprising administering to a mammal in need of such treatment: (1) an effective amount of at least one sterol absorption inhibitor, or pharmaceutically acceptable salt or solvate of the least one sterol absorption inhibitor, or prodrug of the least one sterol absorption inhibitor or pharmaceutically acceptable salt or solvate of the least

one sterol absorption, or mixture thereof; and (2) an effective amount of at least one bile acid sequestrant or other lipid lowering agent.

In another embodiment set forth in Claim 33, Applicants have discovered a method of treating sitosterolemia comprising administering to a mammal in need of such treatment: (1) an effective amount of at least one sterol absorption inhibitor, or pharmaceutically acceptable salt or solvate of the least one sterol absorption inhibitor, or prodrug of the least one sterol absorption or pharmaceutically acceptable salt or solvate of the least one sterol absorption inhibitor, or mixture thereof; and (2) at least one sterol biosynthesis inhibitor.

In another embodiment set forth in Claim 34, Applicants have discovered a method of reducing plasma or tissue concentration of at least one non-cholesterol sterol, 5α-stanol, or mixture thereof, comprising administering to a mammal in need of such treatment an effective amount of at least one treatment composition comprising an effective amount of at least one sterol absorption inhibitor or at least one stanol absorption inhibitor, or pharmaceutically acceptable salt or solvate of the least one sterol absorption inhibitor or the at least one stanol absorption inhibitor, or prodrug of the least one sterol absorption inhibitor or the at least one stanol absorption inhibitor or pharmaceutically acceptable salt or solvate of the least one sterol absorption inhibitor or the at least one stanol absorption inhibitor, or mixture thereof.

In another embodiment set forth in Claim 53, Applicants have discovered a method of reducing plasma or tissue concentration of at least one compound selected from the group consisting of phytosterols, 5α-stanols and mixtures thereof, comprising administering to a sitosterolemic mammal in need of such treatment an effective amount of at least one sterol absorption inhibitor or a prodrug or a pharmaceutically acceptable salt thereof.

In another embodiment set forth in Claim 54, Applicants have discovered a method of reducing plasma or tissue concentration of at least one compound selected from the group consisting of phytosterols, 5α-stanols and mixtures thereof, comprising administering to a mammal in need of such

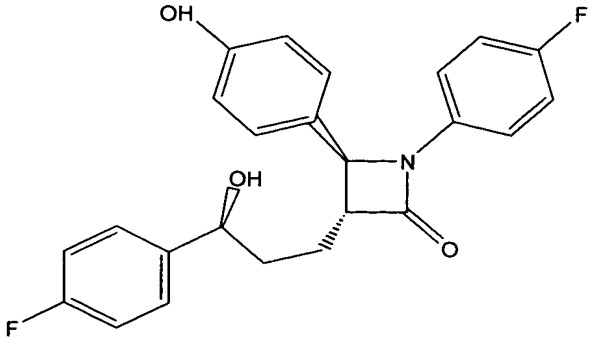
treatment an effective amount of at least one sterol absorption inhibitor or a prodrug or a pharmaceutically acceptable salt thereof and at least one lipid lowering agent.

In another embodiment set forth in Claim 55, Applicants have discovered a method of reducing plasma or tissue concentration of at least one compound selected from the group consisting of phytosterols, 5α-stanols and mixtures thereof, comprising administering to a sitosterolemic mammal in need of such treatment an effective amount of at least one sterol absorption inhibitor or a prodrug or a pharmaceutically acceptable salt thereof and at least one lipid lowering agent.

In another embodiment set forth in Claim 56, Applicants have discovered a method of reducing plasma or tissue concentration of at least one compound selected from the group consisting of phytosterols, 5α-stanols and mixtures thereof, comprising administering to a mammal in need of such treatment an effective amount of at least one sterol absorption inhibitor or a prodrug or a pharmaceutically acceptable salt thereof and at least one bile acid sequestrant.

In the Office Action of July 2, 2003, Applicant was required to elect a species of sterol absorption inhibitor, lipid lowering agent and third therapeutic agent.

Applicant provisionally elected with traverse ezetimibe as the sterol absorption inhibitor, represented by Formula (VIII) below:



(VIII).

Ezetimibe is the active ingredient in ZETIA™ (ezetimibe) pharmaceutical formulation and VYTORIN™ (ezetimibe/simvastatin) pharmaceutical formulation, both of which are commercially available from MSP (Merck Schering-Plough) Pharmaceuticals, Inc. See Response to Restriction Requirement and Election of Species of August 1, 2003 ("Restriction and Election Response") at page 2.

Also, Applicant provisionally elected with traverse cholestyramine as the lipid lowering agent and simvastatin as the third therapeutic agent. See Restriction and Election Response at page 2.

VI

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Has a Prima Facie Case of Obviousness Under 35 U.S.C. § 103 of Claims 1, 8-11, 13-24, 32-45 and 53-56 as obvious over U.S. Patent No. 5,846,966 ("Rosenblum et al.") in view of Belamarich et al. (Pediatrics, 1990; 86(6):977-81) Been Established?

VII

ARGUMENT

The Required Prima Facie Case of Obviousness of Claims 1, 8-11, 13-24, 32-45 and 53-56 Under 35 U.S.C. § 103 Over over U.S. Patent No. 5,846,966 ("Rosenblum et al.") in view of Belamarich et al. (Pediatrics, 1990; 86(6):977-81) Has Failed to be Established

A. The Rejection

Claims 1, 8-11, 13-24, 32-45 and 53-56 have been rejected under 35 U.S.C. §103(a) as obvious over US 5,846,966 ("Rosenblum et al.") in view of Belamarich et al. (Pediatrics, 1990; 86(6):977-81).

The reasons for rejection are set forth in the Final Office Action of February 8, 2005 ("Final Office Action"), summarized as follows:

In the rejection, it is alleged that Rosenblum et al. disclose ezetimibe, with HMG-CoA reductase inhibitors such as simvastatin, as useful for reducing cholesterol and risk of atherosclerosis, as well as dosages for treating hypercholesterolemia. Final Office Action at page 3, lines 22-26.

It is acknowledged in the rejection that Rosenblum et al. do not expressly teach employing ezetimibe with simvastatin, an HMG-CoA

reductase inhibitor and/or cholestyramine, in the dosage herein claimed to treat sitosterolemia. Final Office Action at page 4, lines 3-5.

It is further alleged in the rejection that Belamarich et al. teach that hypercholesterolemia is one of the manifestations of sitosterolemia and that cholestyramine and low sterol diet are effective at lowering both cholesterol and sterol levels in sitosterolemic patients. Final Office Action at page 4, lines 6-10.

In the rejection, it is stated that one of ordinary skill in the art would have been motivated to employ ezetimibe with simvastatin and/or cholestyramine to treat sitosterolemia because Rosenblum et al. teach the combination of ezetimibe and simvastatin to reduce cholesterol. Final Office Action at page 4, lines 11-16. It is alleged that employing the combination of ezetimibe and simvastatin in a method to reduce cholesterol and thereby treat sitosterolemia, a condition known to have elevated cholesterol, would have been reasonably expected to be effective, absent evidence to the contrary. Final Office Action at page 4, lines 16-20.

It is further alleged in the rejection that cholestyramine is known to be effective in lowering cholesterol in sitosterolemic patients and, therefore, administering all three compounds concommitantly for the same purpose would have been obvious to one of ordinary skill in the art, citing In re Kerkoven. Final Office Action at page 4, line 20 – page 5, line 1. Optimization of dosages and regimens is alleged in the rejection to be an optimization of result effect parameters. Final Office Action at page 5, lines 1-3.

In the section of the Final Office Action entitled "Response to Arguments", it is alleged that:

> Hidaka et al. teaches an HMG-CoA reductase inhibitor as effective in treating sitosterolemia [in] that it can reduce the plant sterol level in sitosterolemic patients. Therefore, employing HMG-CoA reductase inhibitor in a method of treating sitosterolemia along with other agents such as those herein claimed would be reasonably expected to be successful and effective.

Also, in the Final Office Action, Applicant's arguments with regard to long felt need were considered but not found persuasive because there was allegedly no showing that others of ordinary skill in the art were working on the problem and, if so, for how long. Final Office Action at page 5, lines 13-16. In the Final Office Action, it was alleged that there is no evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited references, they would still be unable to solve the problem. Final Office Action at page 5, lines 16-19.

In the Final Office Action, it is stated that Applicant's arguments averring certain types of sitosterolemic patients having normal cholesterol levels were considered, but not found persuasive since the arguments are drawn to an unclaimed limitation since the present claims do not exclude any types of sitosterolemic patients. Final Office Action at page 5, line 20 – page 6, line 2.

Also, in the Final Office Action it was stated that Applicant's arguments averring teaching away by Belamarich were considered, but not found persuasive "since HMG-CoA reductase inhibitors, such as pravastatin, was shown to be effective when using in combination with cholestyramine to treat sitosterolemia." Final Office Action at page 6, lines 3-6.

In the Advisory Action of May 20, 2005 ("Advisory Action"), it was stated that Applicant's arguments were considered, but not found persuasive because hypercholesterolemia allegedly is frequently experienced by sitosterolemic patients and treating hypercholesterolemia in sitosterolemic patients would be useful. In the Advisory Action, it is argued that one or ordinary skill in the art would be motivated to treat sitosterolemic patients that also experience hypercholesterolemia and that treating the symptoms of a disease is the same as treating the disease.

Also, in the Advisory Action it was stated that Applicant's arguments regarding long-felt, unfulfilled need was considered deficient because there was no showing that others of ordinary skill in the art were working on the problem and if so, for how long. Further, it is averred in the Advisory Action

that there is no evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the cited references that they would be unable to solve the problem. In the Advisory Action, the Steiner article is argued not to be probative of the issue of long-felt unfulfilled need because the article was published after the filing date of the present application.

B. The Prior Art

Rosenblum et al. disclose that ezetimibe, optionally in combination with an HMG-CoA reductase inhibitor such as simvastatin or lovastatin, is useful for reducing cholesterol and risk of atherosclerosis. Belamarich discloses treatment of a sitosterolemic patient with cholestyramine. See Belamarich et al. Abstract.

C. The Required Prima Facie Case of Obviousness Under 35 U.S.C. § 103 Has Not Been Established

When making a rejection under 35 U.S.C. § 103, the Examiner has the burden of establishing a prima facie case of obviousness. In re Fritch, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992).

The Examiner can satisfy this burden only by showing an objective teaching in the prior art, or knowledge generally available to one of ordinary skill in the art, which would lead an individual to combine the relevant teachings of the references [and/or the knowledge] in the manner suggested by the Examiner. Id.; In re Fine, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

The mere fact that the prior art could be modified does not make the modification obvious *unless the prior art suggests the desirability of the modification* (emphasis added). In re Fritch, 23 U.S.P.Q.2d at 1784; In re Laskowski, 10 U.S.P.Q.2d 1397, 1398 (Fed. Cir. 1989); In re Gordon, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984).

"The ultimate determination of patentability must be based on consideration of the entire record, by a preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence." Manual of Patent Examining Procedure, (Rev. 1, Feb. 2003) § 716.01(d) and In re Oetiker, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992).

Claims 1, 8-11, 13, 14, 34-40 and 53

Claim 1 relates to a method of treating sitosterolemia, comprising administering to a mammal in need of such treatment an effective amount of at least one sterol absorption inhibitor, or pharmaceutically acceptable salt or solvate of the least one sterol absorption inhibitor, or prodrug of the at least one sterol absorption inhibitor or pharmaceutically acceptable salt or solvate of the least one sterol absorption inhibitor, or mixture thereof.

Claim 1 does not require combination with another drug.

Claims 8-11 depend from claim 1 and recite more specific groups of sterol absorption inhibitors. Claims 13 and 14 also depend from claim 1 and recite amounts of sterol absorption inhibitor to be administered.

Claims 34-40 and 53 relate to methods of reducing plasma or tissue concentration of at least one non-cholesterol sterol, 5-α stanol, or mixture thereof by administering a sterol absorption inhibitor to subjects, including to sitosterolemics.

Rosenblum et al. disclose that ezetimibe, optionally in combination with an HMG-CoA reductase inhibitor such as simvastatin or lovastatin, is useful for reducing cholesterol and risk of atherosclerosis. As acknowledged in the Final Office Action at page 4, lines 3-5, *Rosenblum et al. do not suggest or disclose use of ezetimibe, alone or in combination with an HMG-CoA reductase inhibitor or cholestyramine, for treating sitosterolemia* (emphasis added).

Belamarich et al. discloses treatment of a sitosterolemic patient with cholestyramine. See Belamarich et al. Abstract. Belamarich et al. do not teach that hypercholesterolemia is "one of the manifestation[s] of sitosterolemia" as alleged in the Final Office Action, but rather that some sitosterolemics also can have hypercholesterolemia.

Belamarich et al. do not suggest or disclose that ezetimibe or other sterol absorption inhibitors are useful for treating sitosterolemia. Belamarich

et al. do not suggest or disclose that HMG-CoA reductase inhibitors are useful for treating sitosterolemia.

Therefore, neither Rosenblum et al. nor Belamarich et al., taken alone or combined as averred in the rejection, suggest or disclose that ezetimibe or other sterol absorption inhibitors are useful for treating sitosterolemia.

In the "Response to Arguments" section of the Final Office Action, it is alleged that:

> Hidaka et al. teaches an HMG-CoA reductase inhibitor as effective in treating sitosterolemia [in] that it can reduce the plant sterol level in sitosterolemic patients. Therefore, employing HMG-CoA reductase inhibitor in a method of treating sitosterolemia along with other agents such as those herein claimed would be reasonably expected to be successful and effective.

Applicant respectfully disagrees with this characterization of the teachings of Hidaka et al. and respectfully requests that the reference be reviewed again.

In the Hidaka et al. study, the effects of cholestyramine and pravastatin were only evaluated on a single sitosterolemic patient. See Hidaka et al. at page 61, col. 2, lines 8-10. The other patients treated were hypercholesterolemic, *not sitosterolemic*. See Hidaka et al. at page 61, col. 1, line 14 – col. 2, line 7.

Hidaka et al. stated that "[t]he plasma of the [sitosterolemic] patient contained large amounts of plants sterols as well as cholestanol. ***The patient had been treated with cholestyramine, but unfortunately could not tolerate the treatment because of her associated hemorrhoids***. The patient was treated with probucol and pravastatin with her informed consent." See Hidaka et al. at page 61, col. 2, lines 15-20 (emphasis added).

Hidaka et al. further stated "The patient with sitosterolemia ***who could not tolerate cholestyramine*** treatment underwent treatment with other drugs for more than 3 years....***Pravastatin*** (10-20 mg/day) ***administration had little effect on plasma sterol concentrations*** when data from 1991...were used for evaluation ...**sitosterol, 31.8 ± 4.34, 31.0 ± 1.91**" during the

treatment with pravastatin. See Hidaka et al. at page 61, col. 2, lines 24-30 (emphasis added).

Hidaka et al. stated that "***Pravastatin had little effect on plasma sterol levels in a sitosterolemic patient***" and "[t]he ***ineffectiveness of an HMG-CoA reductase inhibitor in lowering plasma sterol concentrations in our sitosterolemic patient as well as in the subjects reported by Nguyen et al....is also difficult to explain***." See Hidaka et al. at page 64, col. 1, lines 43-44 and lines 13-16, respectively (emphasis added). Also, Hidaka et al. disclose that "**Nguyen et al....reported that plasma sterol levels were not lowered by an HMG-CoA reductase inhibitor, lovastatin, in sitosterolemic patients. Our results in a patient with this rare disease mostly agree with theirs**." See Hidaka et al. at page 63, col. 2, lines 16-19, (emphasis added).

Hidaka et al. clearly do **not** teach that an HMG-CoA reductase inhibitor is effective in treating sitosterolemia [in] that it can reduce the plant sterol level in sitosterolemic patients, as alleged in the Final Office Action. Applicant respectfully requests review of the Hidaka et al. reference and correction of this misstatement in the file record.

The conclusion that "employing an HMG-CoA reductase inhibitor in a method of treating sitosterolemia along with other agents such as those herein claimed would be reasonably expected to be successful and effective" is based upon a misinterpretation of the teachings of the Hidaka et al. reference and therefore the prima facie case of obviousness is not properly supported and must be withdrawn.

Clearly, the teachings of Hidaka et al. and others illustrate that compounds that are used to treat hypercholesterolemia (such as pravastatin or lovastatin) may not be effective in treating sitosterolemia. Hidaka et al. clearly discloses that pravastatin was not effective in treating a sitosterolemic patient. Also, Hidaka et al. disclose that "Nguyen et al....reported that plasma sterol levels were not lowered by an HMG-CoA reductase inhibitor, lovastatin, in sitosterolemic patients."

According to L. Nguyen et al., "Regulation of Cholesterol Biosynthesis in Sitosterolemia: Effects of Lovastatin, Cholestyramine, and Dietary Sterol Restriction", 32 J. Lipid Res. (1991) 1941-1948, 1946, "**lovastatin, which is a potent competitive inhibitor of HMG-CoA reductase...did not reduce plasma cholesterol and plant sterols in homozygous sitosterolemic patients**" (emphasis added).

Further, "**[l]ovastatin, a competitive inhibitor of cholesterol biosynthesis that is widely used in the treatment of hypercholesterolemia has been tried but has not been an effective treatment in sitosterolemia**." G. Salen et al., 33 Journal of Lipid Research 945-955, 952 (1992) (emphasis added).

Based upon the foregoing teachings, it would not be obvious to one skilled in the art to administer a compound useful for treating hypercholesterolemia, such as ezetimibe, to a sitosterolemic patient because of the lack of success with conventional hypercholesterolemia treatments as shown in the references above.

In the "Response to Arguments" section of the Final Office Action, it is stated that Applicant's arguments with regard to long-felt need were considered but not found to be persuasive because there was allegedly no showing that others of ordinary skill in the art were working on the problem and, if so, for how long and that there is no evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited references, they would still be unable to solve the problem. Final Office Action at page 5, lines 13-19.

Clearly, the Hidaka et al. and Nguyen et al. references discussed above show that those of ordinary skill in the art were working on the problem of treating sitosterolemia without the deleterious side effects associated with cholestyramine.

Hidaka et al. disclose that treatment of a sitosterolemic patient with cholestyramine was unsuccessful because the patient could not tolerate the treatment because of her associated hemorrhoids. See Hidaka et al. at page

61, col. 2, lines 24-30. Because of the lack of success with cholestyramine, Hidaka et al. evaluated treatment with pravastatin. Hidaka et al. discloses that pravastatin had little effect on plasma sterol levels in a sitosterolemic patient. Id. Nguyen et al. evaluated the effects of treatment with lovastatin for treating sitosterolemia. Nguyen et al. disclose that lovastatin was not effective in treating sitosterolemia. See Nguyen et al. at 1946.

As further evidence of others working on the problem, Hidaka et al. disclose that "Miettinen at al....recently reported that...plasma plant sterol levels tended to be increased during combined treatment with lovastatin and cholestyramine." See Hidaka et al. at page 63, col. 2, lines 8-12. Further, Hidaka et al. disclose that "Nguyen et al....reported that plasma sterol levels were not lowered by an HMG-CoA reductase inhibitor, lovastatin, in sitosterolemic patients. Our results in a patient with this rare disease mostly agree with theirs." See Hidaka et al. at page 63, col. 2, lines 16-19.

The Miettinen references cited by Hidaka et al. were published in 1992 and 1991. The Nguyen et al. references cited by Hidaka et al. were published in 1990 and 1991. The Hidaka et al. reference was published in 1995. The Hidaka et al. reference (and references cited therein) shows the undesirability of cholestyramine as a treatment for sitosterolemia, that the need for alternative treatments has been a persistent one over a number of years that was recognized by those of ordinary skill in the art, and provides evidence of prior unsuccessful attempts to solve the problem using lovastatin and pravastatin. See M.P.E.P § 716.04.

This long-felt need has not been adequately satisfied by another. R. Steiner et al., "Sitosterolemia", http://www.emedicine.com/ped/topic2110.htm (April 5, 2005) (submitted with the Information Disclosure Statement filed April 8, 2005) discloses at page 8 that treatment for sitosterolemia may include dietary changes, pharmacologic agents, and/or surgical intervention. A diet low in plant sterols may be recommended. Bile acid-binding resins may be administered. An ileal bypass may be indicated. At page 9, Steiner et al. disclose that "bile acid-binding resins (e.g., cholestyramine, colestipol) or

competitive inhibitory agents (e.g., sitostanol) could be considered." Treatment with bile acid binding resins is not desirable because of side effects. Ileal bypass surgery is obviously an undesirable treatment.

According to R. Steiner et al. at page 9, "[i]n October 2002, a new cholesterol absorption inhibitor, ezetimibe, received US Food and Drug Administration (FDA) approval for use in sitosterolemia. Because the mechanism by which it inhibits cholesterol absorption is quite specific, the adverse effects and drug interactions associated with the resins should not be expected. A multiple center collaborative randomized placebo-controlled study of ezetimibe 10 mg/d in patients aged 10 years and older determined that ezetimibe was well tolerated and efficacious in reducing plant sterol levels compared with a placebo (Salen, 2004). Limited studies have been conducted on sitostanol in this context. Information on the use of medications other than cholestyramine (and, more recently, ezetimibe) in sitosterolemia is limited; therefore, colestipol and sitostanol cannot generally be recommended."

Thus Hidaka et al. and others have recognized the undesirability of conventional treatments for sitosterolemia, such as cholestyramine. Hidaka et al. and Nguyen et al. disclose unsuccessful attempts to treat sitosterolemia using conventional cholesterol treatments such as pravastatin and lovastatin. R. Steiner et al. disclose that this long-felt need *has been successfully satisfied* by Zetia® ezetimibe formulation (which contains a compound of Formula (VIII) according to the presently claimed invention), *which is approved by the US FDA for treatment of homozygous sitosterolemia*. This treatment avoids the undesirable side effects such as constipation that can occur in sitosterolemic patients taking cholestyramine and avoids the pain and inconvenience of ileal bypass surgery, which are current standard treatments for sitosterolemia.

In the rejection, it is alleged that the Steiner reference is not probative evidence to show long felt need since the article was published after the filing date of the present application. This is incorrect for two reasons. First, the

Steiner reference has been cited to show that those skilled in the art have recognized the success of ezetimibe for treating sitosterolemia and thus provides secondary evidence of non-obviousness. Further this reference is cited to show that the problem of treating sitosterolemia without adverse side effects has persisted for many years, i.e,. long felt need, that was not fulfilled until ezetimibe was used to treat the disease. Therefore, consideration of the Steiner reference is respectfully requested.

Sitosterolemia or phytosterolemia is an inherited disorder in which there is a hyperabsorption of phytosterols (plant sterols such as sitosterol, campesterol, stigmasterol and avenosterol) and shellfish sterols resulting in tendon and tuberous xanthomata. Stedman's Medical Dictionary, 27th Ed. (2000) 1381. Sitosterolemia also can result in accelerated atherosclerosis, hemolytic episodes, arthritis and arthralgias. G. Salen et al. at 945.

In the Advisory Action at page 2, it is alleged that hypercholesterolemia is frequently experienced by sitosterolemics. No reference is provided to support this allegation in the rejection. As shown by Salen, plasma cholesterol concentrations can vary considerably in sitosterolemic subjects. Id. at page 946. As shown in Table 1 of the Salen reference, cholesterol levels in sitosterolemics may be low but are usually increased over age matched controls. Id. One homozygous sitosterolemic patient (subject CL) in Table 1 had a cholesterol level of only 134 mg/dl.

Applicant has shown that there is a long felt unfulfilled need for a treatment for sitosterolemics that inhibits absorption of phytosterols and shellfish sterols without the disadvantages of such treatments as cholestyramine (a bile acid sequestrant) or ileal bypass surgery. Assignee is successfully marketing Zetia™ ezetimibe formulation in the United States for treatment of sitosterolemia.

Neither the teachings of Rosenblum et al. nor those of Belamarich et al., taken alone or combined as set forth in the Office Action, suggest or disclose use of a sterol or 5-α stanol absorption inhibitor, such as ezetimibe, for treatment of sitosterolemia. The Hidaka et al. and Nguyen et al.

references disclose that others have recognized the long-felt need and unsuccessfully attempted to solve the problem using pravastatin and lovastatin (HMG-CoA reductase inhibitors). As discussed above, not all cholesterol treatments are successful for treating sitosterolemia. Neither Rosenblum et al. nor Belamarich et al. provides any guidance as to factors to predict success of cholesterol treatments for treating sitosterolemia. Applicant has shown a long-felt unfulfilled need for a treatment for sitosterolemia with less likelihood of deleterious side effects such as those associated with treatment with cholestyramine. Applicant's invention has successfully met this need, as discussed in detail above.

Therefore, Applicant respectfully requests that the rejection of claims 1, 8-11, 13, 14, 34-40 and 53 under 35 U.S.C. § 103 be reconsidered and withdrawn.

Rejection of claims 15-24, 33, 41, 42, 43, 54 and 55

Generally, claims 15-24, 33, 41, 42, 43, 54 and 55 depend from claims 1 and 39 and further require the presence of at least one lipid lowering agent, such as an HMG-CoA reductase inhibitor (for example simvastatin or lovastatin) with the at least one sterol absorption inhibitor.

As discussed above, Rosenblum et al. disclose that ezetimibe, optionally in combination with an HMG-CoA reductase inhibitor such as simvastatin or lovastatin, is useful for reducing cholesterol and risk of atherosclerosis. As acknowledged in the Final Office Action at page page 4, lines 3-5, *Rosenblum et al. do not suggest or disclose use of ezetimibe, alone or in combination with an HMG-CoA reductase inhibitor or cholestyramine, for treating sitosterolemia* (emphasis added).

Belamarich et al. do not suggest or disclose that ezetimibe or other sterol absorption inhibitors are useful for treating sitosterolemia. Belamarich et al. do not suggest or disclose that HMG-CoA reductase inhibitors are useful for treating sitosterolemia. Belamarich discloses treatment of a sitosterolemic patient with cholestyramine. See Belamarich et al. Abstract.

Belamarich et al. do not teach that hypercholesterolemia is "one of the manifestation[s] of sitosterolemia" as alleged in the Final Office Action, but rather that some sitosterolemics can also have hypercholesterolemia. Belamarich et al. teach away from using an HMG-CoA reductase inhibitor for treating sitosterolemia by noting '[I]t has recently been hypothesized that the hyperabsorption of plant sterols and cholesterol observed in sitosterolemia is a compensatory response to a deficiency of the rate-limiting enzyme of cholesterol biosynthesis, hydroxymethylglutaryl-Co A reductase". One skilled in the art would not be motivated by this disclosure in Belamarich et al. to administer an HMG-Co A reductase inhibitor to a sitosterolemic patient.

Hidaka et al. clearly do not teach that an HMG-CoA reductase inhibitor is effective in treating sitosterolemia [in] that it can reduce the plant sterol level in sitosterolemic patients, as alleged in the Final Office Action. Please see the discussion of this reference above. Applicant respectfully requests that the Hidaka et al. reference be reviewed and this misstatement in the file record be corrected.

The conclusion that "employing an HMG-CoA reductase inhibitor in a method of treating sitosterolemia along with other agents such as those herein claimed would be reasonably expected to be successful and effective" is based upon a misinterpretation of the teachings of the Hidaka et al. reference and therefore the prima facie case of obviousness is not properly supported and must be withdrawn.

Clearly, the teachings of Hidaka et al. and others illustrate that compounds that are used to treat hypercholesterolemia (such as pravastatin or lovastatin) may not be effective in treating sitosterolemia. Hidaka et al. clearly discloses that pravastatin was not effective in treating a sitosterolemic patient. Also, Hidaka et al. disclose that "Nguyen et al....reported that plasma sterol levels were not lowered by an HMG-CoA reductase inhibitor, lovastatin, in sitosterolemic patients." As a further example, "[l]ovastatin, a competitive inhibitor of cholesterol biosynthesis that is widely used in the treatment of hypercholesterolemia has been tried but has not been an effective treatment

in sitosterolemia." G. Salen et al., 33 Journal of Lipid Research 945-955, 952 (1992). Therefore, it would not be obvious to one skilled in the art to administer a compound useful for treating hypercholesterolemia to a sitosterolemic patient.

Neither the teachings of Rosenblum et al. nor those of Belamarich et al., taken alone or combined as set forth in the Office Action, suggest or disclose use of a sterol or 5-α stanol absorption inhibitor, such as ezetimibe, in combination with an HMG-Co A reductase inhibitor for treatment of sitosterolemia. Hidaka et al. shows that pravastatin was not effective in treating sitosterolemia and thus provides no motivation for such a combination. As discussed above, not all cholesterol treatments are successful for treating sitosterolemia. Applicant has shown above a long-felt unfulfilled need for a treatment for sitosterolemia with less likelihood of deleterious side effects such as those associated with cholestyramine treatment. Applicant's invention has successfully met this need, as discussed in detail above.

Therefore, Applicant respectfully requests that the rejection of claims 15-24, 32, 33, 41, 42, 54 and 55 under 35 U.S.C. § 103 be reconsidered and withdrawn.

Rejection of claims 32 and 43-45

Generally, claims 32 and 43-45 relate to methods of treating sitosterolemia using at least one bile acid sequestrant with at least one sterol absorption inhibitor.

As discussed above, Rosenblum et al. disclose that ezetimibe, optionally in combination with an HMG-CoA reductase inhibitor such as simvastatin or lovastatin, is useful for reducing cholesterol and risk of atherosclerosis. As acknowledged in the Final Office Action at page page 4, lines 3-5, *Rosenblum et al. do not suggest or disclose use of ezetimibe, alone or in combination with an HMG-CoA reductase inhibitor or cholestyramine, for*

treating sitosterolemia (emphasis added). Rosenblum et al. do not suggest or disclose use of bile acid sequestrants at all.

Belamarich et al. do not disclose that ezetimibe or other sterol absorption inhibitors are useful for treating sitosterolemia. Belamarich discloses treatment of a sitosterolemic patient with cholestyramine. See Belamarich et al. Abstract. Belamarich et al. do not teach that hypercholesterolemia is "one of the manifestation[s] of sitosterolemia" as alleged in the Final Office Action, but rather that some sitosterolemics can also have hypercholesterolemia. Therefore, it would not be obvious to one skilled in the art to administer a sterol absorption inhibitor compound useful for treating hypercholesterolemia to a sitosterolemic patient.

Hidaka et al. discloses that cholestyramine treatment of a patient was discontinued due to an adverse side effect. Hidaka et al. do not suggest or disclose treatment of sitosterolemia with a sterol absorption inhibitor compound. Hidaka et al. disclose unsuccessful attempts to treat sitoterolemia with other cholesterol treatments, namely pravastatin and lovastatin. Thus, Hidaka et al. provide no motivation for treating a sitosterolemic patient with a bile acid sequestrant and sterol absorption inhibitor compound, since attempts to treat sitoterolemia with other cholesterol treatments, namely pravastatin and lovastatin, were unsuccessful.

Neither the teachings of Rosenblum et al. nor those of Belamarich et al., taken alone or combined as set forth in the Office Action with Hidaka et al., suggest or disclose use of a sterol or 5-α stanol absorption inhibitor, such as ezetimibe, in combination with a bile acid sequestrant for treatment of sitosterolemia. As discussed above, not all cholesterol treatments are successful for treating sitosterolemia. Applicant has shown above a long-felt unfulfilled need for a treatment for sitosterolemia. Applicant's invention has successfully met this need, as discussed in detail above.

Therefore, Applicant respectfully requests that the rejection of claims 32 and 43-45 under 35 U.S.C. § 103 be reconsidered and withdrawn.

Further, Applicant respectfully asserts that the 35 U.S.C. § 103 rejection is based upon improper hindsight reconstruction. The prima facie case of obviousness has not been established. Accordingly, Applicant respectfully request that the § 103(a) rejection of claims 1, 8-11, 13-24, 32-45 and 53-56 be reconsidered and withdrawn.

Respectfully submitted,

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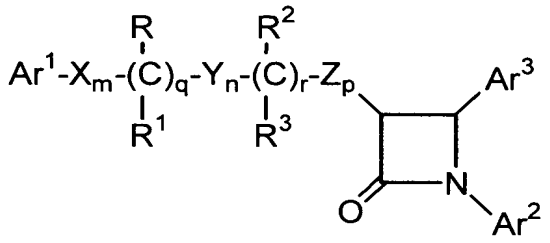
CLAIM APPENDIX

1. A method of treating sitosterolemia, comprising administering to a mammal in need of such treatment an effective amount of at least one sterol absorption inhibitor, or pharmaceutically acceptable salt or solvate of the least one sterol absorption inhibitor, or prodrug of the at least one sterol absorption inhibitor or pharmaceutically acceptable salt or solvate of the least one sterol absorption inhibitor, or mixture thereof.

8. The method of claim 1, wherein the at least one sterol absorption inhibitor is represented by Formula (VII):



(VII)

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (VII) or of the isomers thereof, or prodrugs of the compounds of Formula (VII) or of the isomers, salts or solvates thereof, wherein:

Ar^1 and Ar^2 are independently selected from the group consisting of aryl and R^4-substituted aryl;

Ar^3 is aryl or R^5-substituted aryl;

X, Y and Z are independently selected from the group consisting of -CH_2-,

-CH(lower alkyl)- and -C(dilower alkyl)-;

R and R^2 are independently selected from the group consisting of -OR^6,

-$O(CO)R^6$, -$O(CO)OR^9$ and -$O(CO)NR^6R^7$;

R^1 and R^3 are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1;

r is 0 or 1;

m, n and p are independently 0, 1, 2, 3 or 4;

provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and

provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

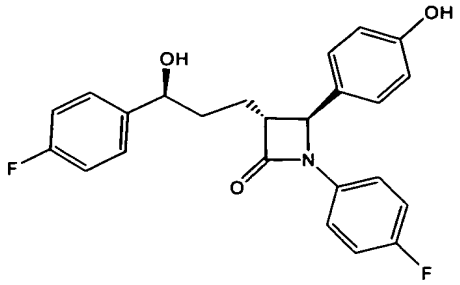
R^4 is 1-5 substituents independently selected from the group consisting of lower alkyl, $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $-S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$, $-CH=CH-COOR^6$, $-CF_3$, $-CN$, $-NO_2$ and halogen;

R^5 is 1-5 substituents independently selected from the group consisting of $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $-S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$ and $-CH=CH-COOR^6$;

R^6, R^7 and R^8 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

R^9 is lower alkyl, aryl or aryl-substituted lower alkyl.

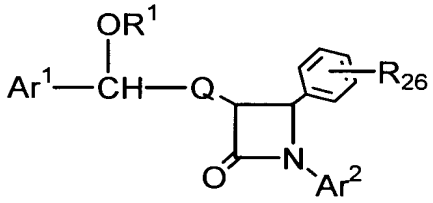
9. The method of claim 1, wherein the at least one sterol absorption inhibitor is represented by Formula (VIII):



(VIII)

or pharmaceutically acceptable salts or solvates of the compound of Formula (VIII) or prodrugs of the compound of Formula (VIII) or of the salts or solvates thereof.

10. The method of claim 1, wherein the at least one sterol absorption inhibitor is represented by Formula (IX):



(IX)

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (IX) or of the isomers thereof, or prodrugs of the compounds of Formula (IX) or of the isomers, salts or solvates thereof, wherein:

R^{26} is selected from the group consisting of:

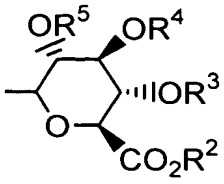
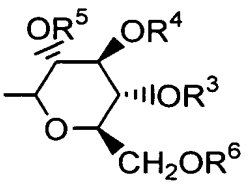
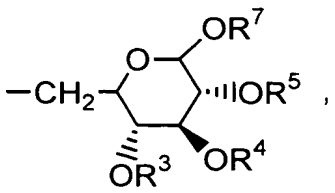
a) OH;

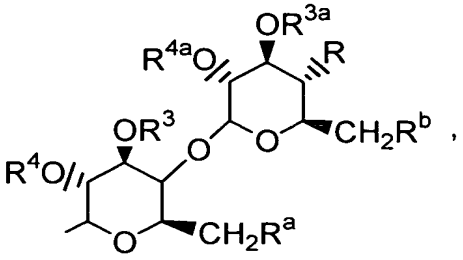
b) OCH_3;

c) fluorine and

d) chlorine.

R^1 is selected from the group consisting of

H,  ,  ,  ,

 , -SO_3H; natural and unnatural amino acids.

R, R^a and R^b are independently selected from the group consisting of H,

-OH, halogeno, $-NH_2$, azido, (C_1-C_6)alkoxy(C_1-C_6)-alkoxy and -W-R^{30};

W is independently selected from the group consisting of -NH-C(O)-, -O-C(O)-, -O-C(O)-N(R^{31})-, -NH-C(O)-N(R^{31})- and -O-C(S)-N(R^{31})-;

R^2 and R^6 are independently selected from the group consisting of H, (C_1-C_6)alkyl, aryl and aryl(C_1-C_6)alkyl;

R^3, R^4, R^5, R^7, R^{3a} and R^{4a} are independently selected from the group consisting of H, (C_1-C_6)alkyl, aryl(C_1-C_6)alkyl, -C(O)(C_1-C_6)alkyl and -C(O)aryl;

R^{30} is independently selected form the group consisting of R^{32}-substituted T, R^{32}-substituted-T-(C_1-C_6)alkyl, R^{32}-substituted-(C_2-C_4)alkenyl, R^{32}-substituted-(C_1-C_6)alkyl, R^{32}-substituted-(C_3-C7)cycloalkyl and R^{32}-substituted-(C_3-C7)cycloalkyl(C_1-C_6)alkyl;

R^{31} is independently selected from the group consisting of H and (C_1-C_4)alkyl;

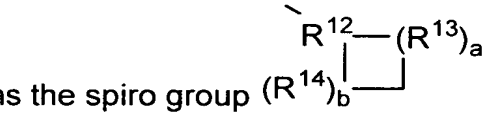
T is independently selected from the group consisting of phenyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, iosthiazolyl, benzothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl and pyridyl;

R^{32} is independently selected from 1-3 substituents independently selected from the group consisting of H, halogeno, $(C_1\text{-}C_4)$alkyl, -OH, phenoxy, $-CF_3$, $-NO_2$, $(C_1\text{-}C_4)$alkoxy, methylenedioxy, oxo, $(C_1\text{-}C_4)$alkylsulfanyl, $(C_1\text{-}C_4)$alkylsulfinyl, $(C_1\text{-}C_4)$alkylsulfonyl, $-N(CH_3)_2$, -C(O)-$NH(C_1\text{-}C_4)$alkyl, -C(O)-$N((C_1\text{-}C_4)alkyl)_2$, -C(O)-$(C_1\text{-}C_4)$alkyl, -C(O)-$(C_1\text{-}C_4)$alkoxy and pyrrolidinylcarbonyl; or R^{32} is a covalent bond and R^{31}, the nitrogen to which it is attached and R^{32} form a pyrrolidinyl, piperidinyl, N-methyl-piperazinyl, indolinyl or morpholinyl group, or a $(C_1\text{-}C_4)$alkoxycarbonyl-substituted pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indolinyl or morpholinyl group;

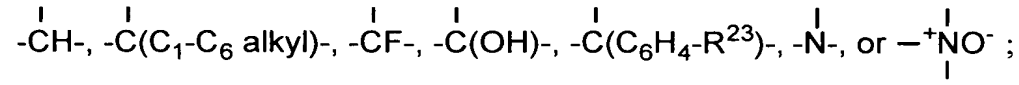
Ar^1 is aryl or R^{10}-substituted aryl;

Ar^2 is aryl or R^{11}-substituted aryl;

Q is $-(CH_2)_q-$, wherein q is 2-6, or, with the 3-position ring carbon of the azetidinone,

forms the spiro group  ;

R^{12} is



R^{13} and R^{14} are independently selected from the group consisting of $-CH_2-$, $-CH(C_1\text{-}C_6$ alkyl)-, $-C(di\text{-}(C_1\text{-}C_6)$ alkyl), -CH=CH- and $-C(C_1\text{-}C_6$ alkyl)=CH-; or R^{12} together with an adjacent R^{13}, or R^{12} together with an adjacent R^{14}, form a -CH=CH- or a $-CH=C(C_1\text{-}C_6$ alkyl)- group;

a and b are independently 0, 1, 2 or 3, provided both are not zero; provided that when R^{13} is -CH=CH- or -C(C_1-C_6 alkyl)=CH-, a is 1; provided that when R^{14} is -CH=CH- or -C(C_1-C_6 alkyl)=CH-, b is 1; provided that when a is 2 or 3, the R^{13}'s can be the same or different; and provided that when b is 2 or 3, the R^{14}'s can be the same or different;

R^{10} and R^{11} are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of (C_1-C_6)alkyl, -OR^{19}, -O(CO)R^{19}, -O(CO)OR^{21}, -O(CH_2)$_{1-5}OR^{19}$, -O(CO)$NR^{19}R^{20}$, -$NR^{19}R^{20}$, -NR^{19}(CO)R^{20}, -NR^{19}(CO)OR^{21}, -NR^{19}(CO)$NR^{20}R^{25}$, -$NR^{19}SO_2R^{21}$, -$COOR^{19}$, -$CONR^{19}R^{20}$, -COR^{19}, -$SO_2NR^{19}R^{20}$, S(O)$_{0-2}R^{21}$,

-O(CH_2)$_{1-10}$-$COOR^{19}$, -O(CH_2)$_{1-10}CONR^{19}R^{20}$, -(C_1-C_6 alkylene)-$COOR^{19}$,

-CH=CH-$COOR^{19}$, -CF_3, -CN, -NO_2 and halogen;

Ar^1 can also be pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl;

R^{19} and R^{20} are independently selected from the group consisting of H, (C_1-C_6)alkyl, aryl and aryl-substituted (C_1-C_6)alkyl;

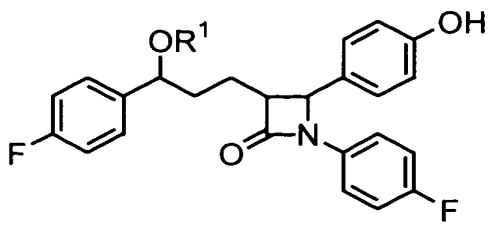
R^{21} is (C_1-C_6)alkyl, aryl or R^{24}-substituted aryl;

R^{22} is H, (C_1-C_6)alkyl, aryl (C_1-C_6)alkyl, -C(O)R^{19} or -$COOR^{19}$;

R^{23} and R^{24} are independently 1-3 groups independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, -COOH, NO_2, -$NR^{19}R^{20}$, -OH and halogeno; and

R^{25} is H, -OH or (C_1-C_6)alkoxy.

11. The method of claim 10, wherein the at least one sterol absorption inhibitor is represented by Formula (X):



X

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (X) or of the isomers thereof, or prodrugs of the compounds of Formula (X) or of the isomers, salts or solvates thereof.

13. The method according to claim 1, wherein the sterol absorption inhibitor is administered to the mammal in an amount ranging from about 0.1 to about 30 milligrams of sterol absorption inhibitor per kilogram of mammal body weight per day.

14. The method according to claim 13, wherein the sterol absorption inhibitor is administered to the mammal in an amount ranging from about 0.1 to about 15 milligrams of sterol absorption inhibitor per kilogram of mammal body weight per day.

15. The method of claim 1, further comprising administering to the mammal in need of such treatment an effective amount of at least one lipid lowering agent in combination with the at least one sterol absorption inhibitor.

16. The method of claim 15, wherein the lipid lowering agent is a HMG-CoA reductase inhibitor.

17. The method of claim 16, wherein the HMG-CoA reductase inhibitor is selected from the group consisting of simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, itavastatin and mixtures thereof.

18. The method of claim 17, wherein the HMG-CoA reductase inhibitor is simvastatin or atorvastatin.

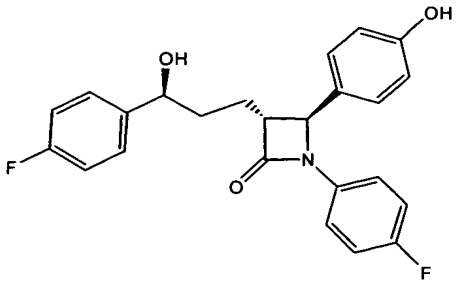
19. The method of claim 15, wherein the sterol absorption inhibitor is administered to the mammal in an amount ranging from about 0.1 to about 30 milligrams of sterol absorption inhibitor per kilogram of mammal body weight per day.

20. The method of claim 15, wherein the lipid lowering agent is administered to the mammal in an amount ranging from about 0.1 to about 80 milligrams of lipid lowering agent per kilogram of mammal body weight per day.

21. The method of claim 15, wherein the sterol absorption inhibitor and lipid lowering agent are present in separate treatment compositions.

22. The method of claim 15, comprising:

a) a sterol absorption inhibitor represented by Formula (VIII):



(VIII)

and

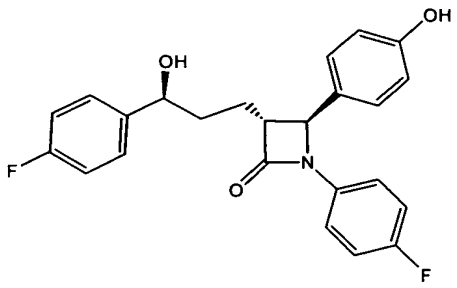
b) at least one HMG-CoA reductase inhibitor.

23. The method of claim 22, wherein the HMG-CoA reductase inhibitor is selected from the group consisting of lovastatin, pravastatin,

fluvastatin, simvastatin, atorvastatin, rosuvastatin, itavastatin and mixtures thereof.

24. A method of treating sitosterolemia comprising administering to a mammal in need of such treatment:

(a) an effective amount of a sterol absorption inhibitor represented by Formula (VIII):



(VIII)

and

b) an effective amount of atorvastatin and/or simvastatin.

32. A method of treating sitosterolemia, comprising administering to a mammal in need of such treatment: (1) an effective amount of at least one sterol absorption inhibitor, or pharmaceutically acceptable salt or solvate of the least one sterol absorption inhibitor, or prodrug of the least one sterol absorption inhibitor or pharmaceutically acceptable salt or solvate of the least one sterol absorption, or mixture thereof; and (2) an effective amount of at least one bile acid sequestrant or other lipid lowering agent.

33. A method of treating sitosterolemia comprising administering to a mammal in need of such treatment: (1) an effective amount of at least one sterol absorption inhibitor, or pharmaceutically acceptable salt or solvate of the least one sterol absorption inhibitor, or prodrug of the least one sterol absorption or pharmaceutically acceptable salt or solvate of the least one

sterol absorption inhibitor, or mixture thereof; and (2) at least one sterol biosynthesis inhibitor.

34. A method of reducing plasma or tissue concentration of at least one non-cholesterol sterol, 5α-stanol, or mixture thereof, comprising administering to a mammal in need of such treatment an effective amount of at least one treatment composition comprising an effective amount of at least one sterol absorption inhibitor or at least one stanol absorption inhibitor, or pharmaceutically acceptable salt or solvate of the least one sterol absorption inhibitor or the at least one stanol absorption inhibitor, or prodrug of the least one sterol absorption inhibitor or the at least one stanol absorption inhibitor or pharmaceutically acceptable salt or solvate of the least one sterol absorption inhibitor or the at least one stanol absorption inhibitor, or mixture thereof.

35. The method according to claim 34, wherein the non-cholesterol sterol is at least one phytosterol.

36. The method according to claim 35, wherein the phytosterol is selected from the group consisting of sitosterol, campesterol, stigmasterol, avenosterol, and mixtures thereof.

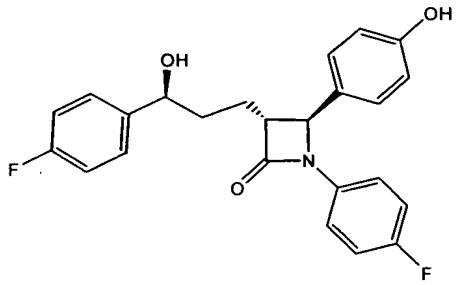
37. The method according to claim 36, wherein the phytosterol is selected from the group consisting of sitosterol and campesterol.

38. The method according to claim 34, wherein the 5α-stanol is selected from the group consisting of cholestanol, 5α-campestanol, 5α-sitostanol and mixtures thereof.

39. A method of reducing plasma or tissue concentration of at least one non-cholesterol sterol, 5α-stanol, or mixture thereof, comprising administering to a sitosterolemic mammal in need of such treatment an

effective amount of at least one treatment composition comprising an effective amount of at least one sterol absorption inhibitor or at least one stanol absorption inhibitor, or pharmaceutically acceptable salt or solvate of the least one sterol absorption inhibitor or the at least one stanol absorption inhibitor, or prodrug of the least one sterol absorption inhibitor or the at least one stanol absorption inhibitor or pharmaceutically acceptable salt or solvate of the least one sterol absorption inhibitor or the at least one stanol absorption inhibitor, or mixture thereof.

40. The method of 39, wherein the sterol absorption inhibitor is represented by Formula (VIII)



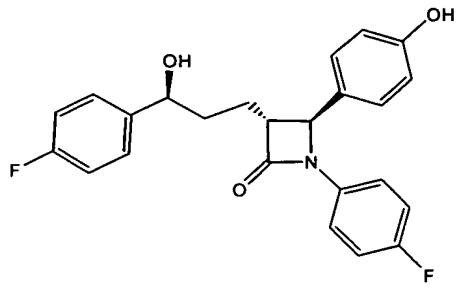
(VIII) .

41. The method of claim 40, wherein the treatment composition further comprises at least one lipid lowering agent which is an HMG-CoA reductase inhibitor.

42. The method of claim 41, wherein the HMG-CoA reductase inhibitor is simvastatin or atorvastatin.

43. The method of claim 39, further comprising administering to the mammal in need of such treatment an effective amount of at least one bile acid sequestrant in combination with at least one of the sterol absorption inhibitors.

44. The method of claim 39, wherein the sterol absorption inhibitor is represented by Formula (VIII)



(VIII)

and the treatment composition further comprises at least one bile acid sequestrant.

45. The method of claim 44, wherein the bile acid sequestrant is selected from the group consisting of cholestyramine, colesevelam hydrochloride, and colestipol.

53. A method of reducing plasma or tissue concentration of at least one compound selected from the group consisting of phytosterols, 5α-stanols and mixtures thereof, comprising administering to a sitosterolemic mammal in need of such treatment an effective amount of at least one sterol absorption inhibitor or a prodrug or a pharmaceutically acceptable salt thereof.

54. A method of reducing plasma or tissue concentration of at least one compound selected from the group consisting of phytosterols, 5α-stanols and mixtures thereof, comprising administering to a mammal in need of such treatment an effective amount of at least one sterol absorption inhibitor or a prodrug or a pharmaceutically acceptable salt thereof and at least one lipid lowering agent.

55. A method of reducing plasma or tissue concentration of at least one compound selected from the group consisting of phytosterols, 5α-stanols

and mixtures thereof, comprising administering to a sitosterolemic mammal in need of such treatment an effective amount of at least one sterol absorption inhibitor or a prodrug or a pharmaceutically acceptable salt thereof and at least one lipid lowering agent.

56. A method of reducing plasma or tissue concentration of at least one compound selected from the group consisting of phytosterols, 5α-stanols and mixtures thereof, comprising administering to a mammal in need of such treatment an effective amount of at least one sterol absorption inhibitor or a prodrug or a pharmaceutically acceptable salt thereof and at least one bile acid sequestrant.

EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

None.

Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818)

FEE TRANSMITTAL For FY 2005

Complete if Known	
Application Number	10/057,629
Filing Date	January 25, 2002
First Named Inventor	Harry R. Davis, et al.
Examiner Name	San Ming R. Hui
Art Unit	1617
Attorney Docket No.	CV01382K/4686-045584

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 500.00

METHOD OF PAYMENT (check all that apply)

☒ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): ____

☐ Deposit Account Deposit Account Number: 23-0650 Deposit Account Name The Webb Law Firm

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☐ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☒ Charge any additional fee(s) or underpayments of fee(s) Under 37 CFR 1.16 and 1.17 ☒ Credit any overpayments

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
		Small Entity		Small Entity		Small Entity	
Application Type	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fees Paid ($)
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 or, for Reissues, each claim over 20 and more than in the original patent	50	25
Each independent claim over 3 or, for Reissues, each independent claim more than in the original patent	200	100
Multiple dependent claims	360	180

Total Claims ____ - 20 or HP = Extra Claims ____ x Fee ($) ____ = Fee Paid ($) ____

HP = highest number of total claims paid for, if greater than 20

Multiple Dependent Claims: Fee ($) ____ Fee Paid ($) ____

Indep. Claims ____ - 3 or HP = Extra Claims ____ x Fee ($) ____ = Fee Paid ($) ____

HP = highest number of independent claims paid for, if greater than 3

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets ____ - 100 = Extra Sheets ____ / 50 = Number of each additional 50 or fraction thereof ____ (round up to a whole number) x Fee ($) ____ = Fee Paid ($) ____

4. OTHER FEE(S)

	Fee Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other: Appeal Brief	500.00

SUBMITTED BY

Signature	[signature]	Registration No. (Attorney/Agent)	35,972	Telephone	412-471-8815
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06/7/05

AF & JFW

PTO/SB/21 (04-04)
Approved for use through 07/31/2006. OMB 0651-0031
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/057,629
Filing Date	January 25, 2002
First Named Inventor	Harry R. Davis et al.
Art Unit	1617
Examiner Name	San Ming R. Hui
Total Number of Pages in This Submission: 41	Attorney Docket Number: CV001382K US – 4686-045584

ENCLOSURES (Check all that apply)

- ☒ Fee Transmittal Form
  - ☒ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Documents
- ☐ Response to Missing Parts/ Incomplete Application
  - ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition to Reinstate
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s)_____
- ☐ After Allowance communication To Technology Center (TC)
- ☐ Appeal Communication to Board Of Appeals and Interferences
- ☒ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☐ Other Enclosure(s) (please identify below)

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Or Individual name	Ann M. Cannoni Webb Ziesenheim Logsdon Orkin & Hanson, P.C.
Signature	
Date	June 6, 2005

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being sent via Express Mail to the USPTO or deposited with the United States Postal Service with sufficient postage in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Typed or printed name	Chris Craig		
Signature	Chris Craig	Date	6/6/2005